Please amend claim 24 to read as follows:

14 ~~24~~ (amended). The method of claim ~~23~~ 13, wherein said polyethylenimine nitrogen:DNA phosphate ratio is 10:1.

Please cancel claims 7, 9-13 and 16

REMARKS

Status of the Claims

Claims 1-24 are pending. Claims 1-24 stand rejected. Claims 1-4, 8, 14-15, 17-18, 21, and 23-24 are amended and claims 7, 9-13 and 16 are canceled herein. Claims 1-4, 15, 18, 21, and 23-24 are amended to overcome rejections. In lieu of the amendment to independent claim 1, claims 8, 14 and 17 are amended to properly depend from amended claim 1 and to correct spelling errors.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendments. The attached page is captioned "**VERSION WITH MARKINGS TO**

SHOW CHANGES MADE". No new matter has been added. Reconsideration of the pending claims is respectfully requested.

The U.S.C. §112 rejections, second paragraph

Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

a. Claim 1 was considered indefinite due to "increasing" with out a recitation of a base reference. Claim 1 is amended to recite that increasing drug deposition is due to the addition of carbon dioxide to the air used for aerosolization of the drug.

b. Claims 1-4 was considered vague and indefinite due to containing a percent value with no units. Claims 1-4 are amended to recite percent by volume carbon dioxide gas.

c. Claims 11 and 14 was considered vague and indefinite due to lack of definition of "sterically stabilized". Claim 11 is canceled herein. Applicants submit that the term "sterically stabilized liposome" is well known in the art. A "sterically stabilized

liposome" is a liposome that has been modified by attaching a polyethylene glycol coat to a modified phospholipid, typically a phosphatidylethanolamine; the pegylation provides a steric barrier that increases the half-life of the liposome. Additionally, the name of a sterically stabilized liposome indicates it is a sterically stabilized liposome and not a conventional or modified liposome as in the instant dimyristoylphosphoethanolamine poly(ethylene glycol) 2000.

d. Claim 18 was considered vague and indefinite due to "derivatives". Claim 18 has been amended to replace "camptothecin derivatives" with 9-nitrocamptothecin.

e. Claims 23-24 was considered vague and indefinite because they contain "nitrogen:phosphate ratio" in polyethylenimine. Claims 23-24 have been amended to recite the ratio of polyethylenimine nitrogen to DNA phosphate as defined in the specification (page 38).

Accordingly, in view of the claim amendments and arguments presented supra, Applcants respectfully request that the rejection of claims 1-24 under 35 U.S.C. § 112, second paragraph be withdrawn.

The U.S.C. §102(e) rejections

Claims 1, 3, 5-6 and 19-22 stand rejected under 35 U.S.C 102(b) as being anticipated by **Densmore, Jr.** *et al.* (U.S. 6,106,859). Applicants respectfully traverse this reaction.

The Examiner states that the **Densmore, Jr.** *et al.* teaches a liposomal aerosol composition, comprising a pharmaceutical compound, a cationic lipid, a neutral co-lipid and a tryptone and further discloses the use of 5% carbon dioxide in aerosolized preparations delivered in 1 minute intervals for enhancing the deep breathing of animals and thereby the drug deposition of the transfection formulations. The formulations may contain DNA or a gene in a plasmid.

The instant application teaches a method of increasing drug delivery to the lungs via aerosolization by aerosolizing the drug with a CO_2-air mixture comprising up to 10% CO_2 by volume. The drugs can be water soluble and thus aerosolized in solution or insoluble/lipophilic drugs aerosolized with a carrier. Administration of the drugs via this CO_2-air mixture is done continuously for up to about 30 minutes or longer.

Applicants have amended claim 1 to recite the aerosolized drug as either soluble or carried by a sterically stabilized liposome, a slow release polymer or a cationic polymer and that administration of the aerosolized drug is continuously delivered via the CO_2-air mixture. As amended, the drug carrier of the instant invention is not the liposome of **Densmore, Jr.** *et al.* The **Densmore, Jr.** *et al.* liposome requires all of a cationic lipid, a neutral lipid and either tryptone or glutamic acid. Furthermore, delivery of the DNA via this liposome is accomplished only after 16 hrs. of intermittent one minute out of every ten minutes exposure to the aerosolized DNA:liposome formulation in 5% CO_2. Additionally, the use of a jet nebulizer to aerosolize a drug or drug-carrier formulation with 5% CO2 for a particular time up to about 30 minutes, including the use of a particular lipid, a particular gene or other drug, are specific features of the deposition method and are, therefore, dependent on the method as recited in the amended claim 1.

Thus, **Densmore, Jr.** *et al.* does not anticipate Applicants' claimed invention. Therefore, as this reference is not

valid prior art against the instant application under 35 U.S.C. §102 and in view of the preceding remarks, Applicants respectfully submit that the cited reference does not anticipate claims 1, 3, 5-6 and 19-22 under 35 U.S.C. §102(b). Accordingly, Applicants respectfully request that the rejection of claims 1, 3, 5-6 and 19-22 under 35 U.S.C. §102(b) be withdrawn.

The U.S.C. §103(a) rejections

Claims 2, 4, 7, and 9-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Densmore, Jr.** *et al.* as applied to claims 1,3,5-6 and 19-22 above and in view of **Knight** et al. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Densmore, Jr.** *et al.* as applied to claims 1,3,5-6 and 19-22 above and in view of **Waldrep** et al. (U.S. 5,958,378).

Densmore, Jr. *et al.* is discussed *supra*. **Knight** et al. teaches small particle liposome or lipid complex aerosol compounds and methods of treatment, which involves lipid or water soluble anti-cancer drugs incorporated into liposomes or other lipid

complexes. **Knight** et al. teaches a conventional or synthetic liposome, e.g., dilauroylphosphatidycholine, to deliver anticancer drugs such as camptothecin and paclitaxol and the method of making said liposome-drug formulations. Although **Knight** et al. mention lipid complexes in conjunction with liposomes, the lipid complexes are neither defined nor described, nor is their method of making disclosed in the specification.

As stated, Applicants have amended claim 1 to recite aerosolization of either soluble drugs in buffer or water or insoluble/lipophilic drugs carried by a sterically stabilized liposome, a slow release polymer or a cationic polymer using a carbon dioxide-air mixture for aerosolization. As **Knight** et al. teaches liposomal aerosol delivery in air of both hydrophilic and hydrophobic anti-cancer drugs, there is no suggestion for one to aerosolize a buffer soluble drug not incorporated within a liposome by the method of **Densmore, Jr.** *et al.* using 5% carbon dioxide in air.

Although the Examiner may argue that one of ordinary skill in the art may be motivated to incorporate anticancer drugs into conventional or synthetic liposomes as disclosed in **Knight** *et al.* and

aerosolize them using 5% CO_2 in air as disclosed in **Densmore, Jr.** *et al.*, such an artisan would not be motivated to use a sterically stabilized liposome. As defined *supra*, a sterically stabilized liposome is significantly different from a conventional liposome in its construction. Despite identifying dimyristoylphosphatidylcholine as a natural or synthetic lecithin useful for making conventional or synthetic liposomes, there is neither a suggestion that such a phospholipid can be modified itself to the phosphotidylethanolamine and subsequently stabilized through pegylation of the outer bilayer surface to form dimyristylphosphoethanolamine poly(ethylene glycol) 2000, as in the instant invention, nor how to do so for any subsequent aerosolization and nebulization procedure with or without carbon dioxide enhancement of delivery nor is there any reasonable expectation that such a method would be successful if undertaken.

Also, the slow release polymers and polycationic polymers of the instant invention, e.g., poly(lactic acid-co-glycolic acid) (PLGA) or polyethyleneimine (PEI) are structurally and chemically significantly different from the liposomes of **Knight** *et al.*

and typically interact with polynucleotides such as DNA. These compounds are not lipids and do not encapsulate, nor incorporate into a bilayer structure, a drug or polynucleotide like a liposome encapsulates such compounds. Rather, depending on the degree of polymerization and overall positive charge carried thereon, a polycationic polymer interacts with the polynucleotide, neutralizes the negative charge carried by the polynucleotide and functions as a carrier of the subsequently condensed polynucleotide. Neither does a slow release polymer form a liposomal like structure, but rather is matrix-like, incorporating the drug therein.

Waldrep *et al.* teaches high dose pharmaceutical liposome aerosol compositions. These compositions comprise a phospholipid such as dilauroylphosphatidycholine and an anti-inflammatory glucocorticoid, e.g., cyclosporin A or budesonide, used for treatment of asthma and other inflammatory lung diseases. These are conventional or synthetic liposomes and are very similar to those taught in **Knight** *et al.* Thus, for the same reasons as disclosed *supra*, one would not be motivated by **Waldrep** *et al.* to formulate a glucocorticoid or other anti-inflammatory, anti-microbial

or anti-viral agents with the carriers of the instant invention for aerosol delivery with 5% carbon dioxide as in **Densmore, Jr.** *et al.*

In view of the above remarks, Applicants respectfully submit that obviousness can not be established by combining the teachings of the prior art absent some teaching, suggestion or motivation supporting the combination to do so. The prior art cited herein does not suggest that one of ordinary skill in the art would have success in using the methods disclosed in the prior art in order to use carbon dioxide to increase deposition in the lungs of either a soluble drug aerosolized without a carrier or an aerosolized insoluble/lipophilic drug carried by a sterically stabilized liposome, a slow release polymer or a polycationic polymer. Indeed, there is no motivation to even try such drug formulations. Thus the invention as a whole was not prima facie obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicants respectfully request that the rejection of claims 2, 4, 7, 8, and 9-18 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed July 10, 2001. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution. Should any fees be due, please debit Deposit Account 07-1185 on which the undersigned is allowed to draw.

Respectfully submitted,

Date: Oct 17, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend claim 1 as follows:

1 (amended). A method of increasing the deposition of ~~aerosolized~~ a drug ~~in~~ into the respiratory tract of an individual or animal during inhalation therapy, comprising the steps of:

mixing carbon dioxide gas with air to form a carbon dioxide-air mixture, said carbon dioxide-air mixture containing up to about 10% by volume carbon dioxide gas;

aerosolizing said drug in said carbon dioxide-air mixture wherein prior to aerosolization said drug is a soluble drug dissolved in a buffered solution or water or, in the alternative, said drug is an insoluble or lipophilic drug carried by a sterically stabilized liposome, a slow release polymer or a polycationic polymer; and

administering said aerosolized drug during inhalation therapy by continuously flowing said carbon-dioxide-air mixture wherein carbon dioxide in said mixture increases inhalation rate and inhaled volume of said aerosolized drug thereby increasing

deposition of said aerosolized drug into the respiratory tract ~~in an air mixture containing up to about 10% carbon dioxide gas~~.

Please amend claim 2 as follows:

2 (amended). The method of claim 1, wherein said air mixture contains 2.5% by volume carbon dioxide gas.

Please amend claim 3 as follows:

3 (amended). The method of claim 1, wherein said air mixture contains 5% by volume carbon dioxide gas.

Please amend claim 4 as follows:

4 (amended). The method of claim 1, wherein said air mixture contains 7.5% by volume carbon dioxide gas.

Please amend claim 8 as follows:

8 (amended). The method of claim ~~7~~ 1, wherein said water soluble or buffer soluble drug is selected from the group consisting of an antibiotic, a ~~mucolytic~~ mucolytic, a bronchodilator, a parasympathetic agent, an enzyme and an anti-viral.

Please amend claim 14 as follows:

14 (amended). The method of claim ~~11~~ 1, wherein said sterically stabilized liposome is a poly(ethylene glycol) modified phospholipid.

Please amend claim 15 as follows:

15 (amended). The method of claim 14, wherein said poly(ethylene glycol) modified phospholipid is dimyristoylphosphoethanolamine poly(ethylene glycol) 2000.

Please amend claim 17 as follows:

17 (amended). The method of claim ~~16~~ 1, wherein said lipophilic drug is selected from the group consisting of amphotericin B, nystatin, glucocorticoids, an immunosuppressive and an anti-cancer drug.

Please amend claim 18 as follows:

18 (amended). The method of claim 17, wherein said anti-cancer drug is selected from the group consisting of

camptothecin, ~~camptothecin derivatives~~ 9-nitrocamptothecin, and paclitaxel.

Please amend claim 21 as follows:

21 (amended). The method of claim 19, wherein said DNA gene is delivered via a polycationic polymer carrier ~~or a cationic liposome~~.

Please amend claim 23 as follows:

23 (amended). The method of claim 22, wherein the ratio of ~~said~~ polyethylenimine nitrogen to DNA phosphate ~~has a~~ (nitrogen:phosphate) ~~ratio of~~ is about 10:1 to about 20:1.

Please amend claim 24 as follows:

24 (amended). The method of claim 23, wherein said polyethylenimine ~~has a~~ nitrogen:DNA phosphate ratio ~~of~~ is 10:1.

Please cancel claims 7, 9-13 and 16